Effects of Radiation on Incidence of Primary Liver Cancer among Atomic Bomb Survivors

John B. Cologne,[a] Shoji Tokuoka,[c] Gilbert W. Beebe,[d] Toshiyuki Fukuhara[e] and Kiyohiko Mabuchi[b]

[a] *Department of Statistics,* [b] *Department of Epidemiology, and* [c] *Consultant, Radiation Effects Research Foundation, 5-2 Hijiyama Park, Minami-ku, Hiroshima, Japan 732-0815;* [d] *Radiation Epidemiology Branch, Division of Cancer Etiology and Genetics, National Cancer Institute, EPN 400, Bethesda, Maryland 20892; and* [e] *Department of Pathology, Hiroshima Prefectural Hospital, Hiroshima, Japan*

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We describe the radiation risk for primary liver cancers between 1958 and 1987 in a cohort of atomic bomb survivors in Hiroshima and Nagasaki, Japan. The analysis is based on a comprehensive pathology review of known or suspected liver neoplasms that generated 518 incident, first primary cases, mostly hepatocellular carcinoma. Excess relative risk from atomic bomb radiation was linear: 0.81 per sievert weighted liver dose (95% CI [0.32, 1.43]; $P < 0.001$). Males and females had similar relative risk so that, given a threefold higher background incidence in males, the radiation-related excess incidence was substantially higher in males. Excess risk peaked for those with age at exposure in the early 20s; there was essentially no excess risk in those exposed before age 10 or after age 45. Whether this was due to a difference in sensitivity or possible confounding by other factors could not be addressed retrospectively in the full cohort. A paucity of cholangiocarcinoma and hemangiosarcoma cases suggested that they are not significantly associated with whole-body radiation exposure, as they are with the internal α-particle-emitting radiological contrast medium Thorotrast. Because most of the radiation-related excess cases occurred among males, it is important to ascertain what factors put men at greater risk of radiation-related liver cancer. © 1999 by Radiation Research Society

INTRODUCTION

It is important to ascertain the risk of liver cancer among atomic bomb survivors in Hiroshima and Nagasaki for various reasons. First, radiation has been linked to liver cancer, but evidence of a radiation effect in the atomic bomb survivors was inconclusive until recently (*1*). Second, liver cancer is one of the most frequent types of cancer in Japan and has displayed a recent rise in incidence (*2*). Thus atomic bomb survivors may be at especially high risk for liver cancer if the excess risk operates multiplicatively on the recently increasing background rate. Characterizing the risk is also important for purposes of radiation protection.

Liver cancer includes hepatocellular carcinoma, hepato-

blastoma, intrahepatic bile duct carcinomas (including cholangiocarcinoma), and hemangiosarcoma. Internal α-particle irradiation from Thorotrast—used as a radiological contrast medium decades ago—is a known liver carcinogen (*3–5*), resulting in cholangiocarcinoma, hepatocellular carcinoma, and hemangiosarcoma (*6–8*). The atomic bomb survivors were exposed to low-linear energy transfer (LET) γ radiation and neutrons. Earlier studies of the atomic bomb survivors using smaller case series were negative or inconclusive regarding the risk for liver cancer from radiation (*9–13*), and there was no information on liver cancer subtype. A new program of study was therefore planned to clarify the risk of liver cancer in the atomic bomb survivor population based on longer follow-up and diagnostic review.[1]

Earlier analyses in the survivors had been based on cause of death recorded on death certificates, which can be inaccurate for liver cancer due in part to frequent metastases from other sites (*14*). Metastases to the liver from radiation-sensitive tissues could induce a spurious relationship with radiation. This diagnostic difficulty was partly overcome in an analysis of the incidence of first primary cancer among the atomic bomb survivors (*1*), which provided the first strong evidence of a radiation-related increase in the incidence of liver cancer in the survivors. Although it used data from Hiroshima and Nagasaki tumor registries that includes histological or clinical diagnoses, that analysis was not based on uniform pathological verification of primary liver cancer, nor did it allow for possible misclassification in the large proportion of death-certificate-only (DCO) cases of liver cancer except through exclusion of all DCO cases. Excluding DCO cases prohibits accurate estimation of incidence, but including them may lead to bias due to diagnostic misclassification.

To obtain the most valid case definition, we conducted an extensive pathology review of known or suspected cases of liver cancer. In this report we describe in-depth analyses of the dose response for atomic bomb radiation, including effects of gender and age at exposure to radiation based on the results of that review.

TABLE 1
Inclusion of Subjects and Liver Cancer Cases in the Incidence Analysis

Sample size (no. of accepted cases)		Numbers excluded	Reason for exclusion
120,321[a] (830) ⇓	→	26,580 (187)	Not in city at the time of the bomb[b]
93,741 (643) ⇓	→	7,109 (43)	Unknown dosimetry[c]
86,632 (600) ⇓	→	262 (3)	Whole-body kerma dose estimate >4 Gy[d]
86,370 (597) ⇓	→	6,476 (84)	Death or cancer occurred prior to initiation of follow-up or cancer diagnosed outside the catchment areas[e] or not a first primary cancer[e]
79,894 (518)			

[a] In the entire Life Span Study (LSS) population (referred to as the LSS-E85).

[b] Persons not in the city at the time of the bombing were excluded because their overall patterns of mortality and cancer incidence differ from those who were in city, due to major differences in socioeconomic and lifestyle factors (based on unreported analyses of LSS survey data).

[c] Due to inadequate information on location and/or shielding at the time of the bombings, radiation dose (according to the latest system, DS86) could not be estimated.

[d] Persons with whole-body kerma dose estimates greater than 4 Gy were excluded from the analysis because of possible large errors in dosimetry.

[e] Only the case status was excluded for these causes; the individual still contributed person time up until the time of first cancer diagnosis.

METHODS

Definition of the Study Population

We used population-based follow-up of the extended Life Span Study (LSS) cohort of atomic bomb survivors in Hiroshima and Nagasaki, Japan (15) at the Radiation Effects Research Foundation (RERF). This cohort consists of about 90,000 persons who were present at the time of one (and only one) of the bombings in 1945 and who were alive and residents of either city at the time of a national census in 1950. (About 26,000 persons, the so-called not-in-city group, who were bona fide residents but were not in either city at the time of the bombings, were excluded from analysis.) Deaths were ascertained with virtual completeness throughout Japan using the Japanese family registry (koseki) system. Cause of death was obtained from death certificates. Cancer incidence data were retrieved from the Hiroshima and Nagasaki tumor and tissue registries. Emigration from Japan could be detected through the koseki; emigrants (less than 1% of the LSS cohort) were excluded from the analyses. We could not monitor residence in the tumor registry catchment areas (Hiroshima and Nagasaki prefectures) on an individual basis for each LSS member, so rather than restricting the study population to residents of the catchment areas, we adjusted the person-time denominators for estimation of cancer incidence as described below. People whose estimated whole-body dose was less than 0.005 Gy were assigned doses of 0 and are referred to here as "zero-dose" persons, but it should be kept in mind that these are exposed survivors whose estimated kerma dose is merely less than 0.005 Gy.

The beginning of follow-up in the current investigation was January 1, 1958, the time at which both the Hiroshima and Nagasaki tumor registry data became available. All persons who were alive and had no known history of cancer at the beginning of 1958 were followed until the earliest of date of first cancer diagnosis, date of last successful koseki retrieval or death, or end of the study period (December 31, 1987). Follow-up was ended in 1987 to allow for nearly complete case reporting at the beginning of our investigation. Gathering of materials for the review (many had to be obtained through special arrangement with local medical institutions) and the review itself each took several years to complete. The results of the pathology review were evaluated thoroughly before we initiated the incidence analyses described here.

The number of persons used in the analysis was 79,894. A detailed description of eligibility criteria and numbers of persons included is shown in Table 1. Persons whose radiation dose (described later) could not be estimated were excluded. Because of suspected large uncertainties in estimating dose to highly exposed persons, 262 persons with assigned doses greater than 4 Gy whole-body kerma—a value thought to be inconsistent with survival—were also excluded. Regression bias caused by imprecision in radiation dose estimates was dealt with as described below in the section on Analytical Methods.

Case Selection and Pathology Review

All cases of known or suspected neoplasms of the liver and biliary system, whether benign, malignant or of an unspecified nature, underwent pathology review. Because liver cancer is often unrecognized at the time of death, these were supplemented by cases of potentially related underlying causes of death, including chronic hepatitis and cirrhosis; other disorders of the liver, gallbladder and biliary tract; all diseases—including cancer—of the pancreas; and all deaths listed only as "cancer of the respiratory or digestive system". Cases meeting these criteria were identified through death certificates, the tumor and tissue registries, the RERF autopsy and surgical-pathology programs,[2] and records of the RERF biennial clinical examination program—the Adult Health Study (AHS), a

[2] Research plan for joint ABCC-NIH pathology studies in Hiroshima and Nagasaki. Technical Report 12-62, Radiation Effects Research Foundation, Hiroshima.

subset of the LSS cohort. In all, 3,902 cases were reviewed by three expert pathologists as described elsewhere.[3]

Only cases accepted as primary liver cancer by the pathologists and diagnosed during the study period were eligible for analysis. A number of cases had no information for review apart from the death certificate; these were dealt with as described below. Cases of primary liver cancer that were not the first occurrence of cancer in an individual were censored at the time of first cancer diagnosis. Second and subsequent primary cancers may result from therapy administered for prior cancer, so that there is a possible bias in radiation effect due to the radiation-related risk of first primary cancer (*1*). Because there was no active cancer ascertainment for the LSS cohort outside of Hiroshima and Nagasaki prefectures (apart from death certificate acquisition) and person-time denominators of incidence rates were adjusted for migration, we ignored all cases (including those identified through death certificates) identified outside of those two prefectures.

Analytical Methods

We applied standard methods for incidence analysis based on Poisson regression in person-year tables (*16–18*) using the same age, time, dose and age-at-exposure strata as in the previous incidence analysis (*1*): 5-year age, calendar-year and age-at-exposure strata and 11 radiation dose categories. These strata are sufficiently narrow that the assumption of constant hazard within each person-time stratum did not preclude smoothly estimating age, time and dose trends. Time since exposure was also grouped into 5-year intervals.

The response to atomic bomb radiation was fitted using weighted liver dose in sieverts based on Dosimetry System 86 (DS86; ref. *19*). The DS86 system estimates organ dose from γ rays and neutrons based on physical calculations of yield coupled with individual data on shielding by buildings, terrain and body tissue. We assumed a quality factor (RBE) of 10 for neutrons to allow for their differential effectiveness. Actual RBE may vary by dose, but precise values for liver are unknown. Previously published statistical methods were used to reduce the risk regression bias due to imprecision (random uncertainties) in the DS86 estimates (*20*); in particular, the lognormal distribution with 35% coefficient of variation for random errors was employed.

We modeled the dose response using excess relative risk (ERR) functions. The general ERR model for cancer incidence may be defined as follows, where c is city, s is gender, a is age at risk (attained age), y is calendar time (year), d is radiation dose, e is age at exposure, and t is time since exposure:

$$\lambda_{c,s}(a,y,d,e,t) = \lambda_{c,s}^0(a,y)[1 + \phi(s,e,t)\mathrm{ERR}_\beta(d)].$$

The symbol β represents parameters of the dose–response function. The functions $\lambda_{c,s}^0(a,y)$, $\mathrm{ERR}_\beta(d)$, and $\phi(s,e,t)$ can take any mathematical form. We used models log-linear in the parameters to fit smooth functions in age and time to describe the background incidence $[\lambda_{c,s}^0(a,y)]$. We examined polynomial ERR functions of dose: $\mathrm{ERR}_\beta(d) = (\beta_1 d + \beta_2 d^2)$. We modeled effect modification $[\phi(s,e,t)]$ as a log-linear function multiplying the ERR. Analyses by subtype used competing risk extensions to Poisson regression methodology (*21*). Statistical tests and confidence limits were likelihood-based, the latter at the 95% level. All analyses were performed using the Epicure software package (Hirosoft International Corporation, Seattle, WA). Models were selected based on successive likelihood ratio tests for adding terms first to the background portion, then to the dose–response portion, then finally to the effect modification terms. Once a final model was obtained, the significance of each term was again checked by a likelihood ratio test for its removal from the model.

[3] T. Fukuhara, G. B. Sharp, T. Mizuno, H. Itakura, M. Yamamoto, M. Tokunaga, S. Tokuoka, J. B. Cologne, G. W. Beebe, Y. Fujita, M. Soda and K. Mabuchi, Hepatocellular carcinoma, cholangiocarcinoma, and hemangiosarcoma among atomic bomb survivors in Hiroshima and Nagasaki, Japan: relationships with radiation, hepatitis B and C. Manuscript currently under RERF internal review.

Migration away from Hiroshima and Nagasaki prefectures was handled by reducing person-year denominators using previously calculated gender-, age- and city-dependent migration probabilities obtained from the AHS subset of the cohort.[4] The resulting denominators estimate the real population-time configuration of persons at risk in the two areas; the actual denominators are not known because detailed information on residency is not available for the entire cohort.

Cases identified through death certificates only could have been metastases from other sites, so it is likely that a number of deaths attributed to liver cancer among the DCO subset did not reflect primary liver cancer. To estimate overall death certificate accuracy for primary liver cancer, others have used cases with both pathological review and liver cancer as cause of death on the death certificate (*14*). We extended that approach by estimating the accuracy (proportion correct) of death certificate diagnoses as a function of calendar period, age at death, and gender using logistic regression and using the estimated accuracy to weight the contribution of DCO cases to the incidence analysis. No adjustment was made for underascertainment (false negatives) because there were sparse numbers of accepted cases detected among other individual cause-of-death categories apart from liver cancer.

After adjustment for city, gender, age, etc., plots of the radiation dose response and age-at-exposure effect were constructed from the fitted parameters using, as a way of verifying adequacy of the model, point estimates and confidence intervals for the abscissa variable grouped into broad categories with all other parameters estimated according to the model. The grouped points in these plots, although providing some indication of the goodness of fit of the statistical model, should not be regarded as valid risk estimates in their own right because of the arbitrary nature of cutpoint selection and natural statistical variation between groups.

RESULTS

A total of 830 primary liver cancer cases were accepted by the pathology review panel as occurring during the study period. From these, 518 cases satisfied the eligibility criteria of Table 1: 382 (74%) based on histological and/or clinical records and 136 (26%) on DCO. Of 364 cases for which subtype could be verified, there were 307 hepatocellular carcinomas, 53 cholangiocarcinomas, 2 mixed hepatocellular/cholangiocarcinomas, and one each of hepatoblastoma and hemangiosarcoma. Numbers of cases and person-years of observation are displayed in Appendix I and Table 2 for broad categories of age, time, radiation dose and age at exposure to provide an overall description of the available data. Actual stratifications used in the analysis are too numerous to show, but the complete person-time table can be provided upon request.

Background Incidence of Liver Cancer

Death certificate errors. Weighting by DCO accuracy in the incidence analysis resulted in an effective reduction from 136 to 63 DCO cases, or from 518 to 445 total cases. The proportion of total DCO cases effectively used in the incidence analysis (as a result of the weighting) increased throughout the study period, from 5 out of 33 (15%) prior to 1965 to 22 out of 27 (81%) at the end of the study,

[4] R. Sposto and D. L. Preston, Correcting for catchment area nonresidency in studies based on tumor-registry data. Technical Report CR1-92, Radiation Effects Research Foundation, Hiroshima.

TABLE 2
Total Number of Primary Liver Cancer (Hepatocellular Carcinoma, Cholangiocarcinoma)[a] Cases
and Migration-Adjusted Person Years (PY) by Radiation Dose and Effect-Modifying Factors
(Gender and Age at Exposure)

Age at exposure		Weighted liver dose (d; Sv)					
		0	$0 < d \leq 0.1$	$0.1 < d \leq 1.0$	$1.0 < d \leq 2.0$	$d > 2.0$	Total
Males							
0–9	Cases	8 (3,0)	3 (3,0)	0	1 (1,0)	0	12 (7,0)
	PY	73,133.1	83,813.6	30,855.9	3,045.96	1,076.35	191,925
10–19		28 (15,0)	41 (16,2)	16 (16,0)	6 (2,0)	1 (1,0)	92 (43,2)
		71,292.5	68,816.7	28,167.4	4,302.81	1,600.29	174,180
20–29		19 (9,0)	11 (2,0)	14 (8,1)	3 (3,0)	2 (1,0)	49 (23,1)
		23,486.0	21,551.6	9,944.51	1,804.71	247.244	57,034.1
30–39		32 (19,0)	28 (12,3)	10 (2,0)	2 (0,0)	2 (1,0)	74 (34,3)
		34,884.2	30,020.5	15,339.1	2,164.30	436.597	82,844.8
40+		40 (16,3)	36 (12,3)	26 (14,2)	0	1 (0,0)	103 (42,8)
		52,167.2	49,654.9	24,277.5	3,013.07	618.273	129,731
Total		127 (62,3)	119 (45,8)	66 (33,3)	12 (6,0)	6 (3,0)	330 (149,14)
		254,963	253,857	108,584	14,330.9	3,978.75	635,714
Females							
0–9		2 (2,0)	1 (0,0)	0	0	0	3 (2,0)
		77,657.8	89,105.2	33,662.9	2,931.10	1,124.66	204,482
10–19		7 (2,0)	9 (5,0)	1 (0,0)	0	0	17 (7,0)
		90,441.2	84,509.9	41,393.7	5,271.73	1,949.17	223,566
20–29		6 (1,1)	9 (3,0)	7 (5,0)	2 (0,0)	0	24 (9,1)
		81,451.9	84,162.4	39,042.1	4,274.00	1,423.53	210,354
30–39		32 (14,1)	15 (2,2)	7 (0,0)	0	1 (0,0)	55 (16,3)
		73,141.8	82,003.7	37,990.1	3,850.17	757.039	197,743
40+		39 (9,9)	23 (6,1)	26 (7,4)	0	1 (1,0)	89 (23,14)
		82,151.9	87,491.9	40,825.9	3,038.20	901.359	214,409
Total		86 (28,11)	57 (16,3)	41 (12,4)	2 (0,0)	2 (1,0)	188 (57,18)
		404,845	427,273	192,915	19,365.2	6,155.75	1,050,553
Both genders combined							
0–9		10 (5,0)	4 (3,0)	0	1 (1,0)	0	15 (9,0)
		150,791	172,919	64,518.8	5,977.06	2,201.01	396,407
10–19		35 (17,0)	50 (21,2)	17 (9,0)	6 (2,0)	1 (1,0)	109 (50,2)
		161,734	153,327	69,561.0	9,574.55	3,549.46	397,745
20–29		25 (10,1)	20 (5,0)	21 (13,1)	5 (3,0)	2 (1,0)	73 (32,2)
		104,938	105,714	48,986.6	6,078.72	1,670.77	267,388
30–39		64 (33,1)	43 (14,5)	17 (2,0)	2 (0,0)	3 (1,0)	129 (50,6)
		108,026	112,024	53,329.3	6,014.47	1,193.64	280,588
40+		79 (25,12)	59 (18,4)	52 (21,6)	0	2 (1,0)	192 (65,22)
		134,319	137,147	65,103.3	6,051.27	1,519.63	344,140
Total		213 (90,14)	176 (61,11)	107 (45,7)	14 (6,0)	8 (4,0)	518 (206,32)
		659,808	681,130	301,499	33,696.1	10,134.5	1,686,268

[a] Subtype was not known for all cases because many were based on clinical diagnosis or death certificate only.

suggesting an improvement in death certificate diagnoses of liver cancer with year.

Age, period, city and gender. Given the demographics of the LSS cohort, the overall background incidence of liver cancer was 24.9 [22.4, 27.6] per 100,000 person-years but was best described by gender-specific age trends and city-specific calendar-year trends (Appendix II). Gender-by-city, gender-by-year and city-by-age interactions were not apparent.

The overall incidence of liver cancer was 3.3 (CI: [2.7, 4.0]) times higher in males than females. Incidence in males rose rapidly with age after age 40 but did not change substantially after age 60. There was a much slower rise in incidence in females with age that began later (around age 50). Peak incidence among males occurred around age 70; incidence did not peak with age among females.

Crude incidence was similar in the two cities: Relative incidence in Nagasaki compared to Hiroshima was 0.94 [0.77, 1.15] ($P > 0.5$). However, age-adjusted incidence differed substantially between the two cities with respect to calendar time. In the earlier part of the study, incidence was higher in Nagasaki, but the difference narrowed with time and became higher in Hiroshima in the late 1970s. Around 1980 incidence in both cities began increasing; by 1987 it was more than double the levels prior to 1970.
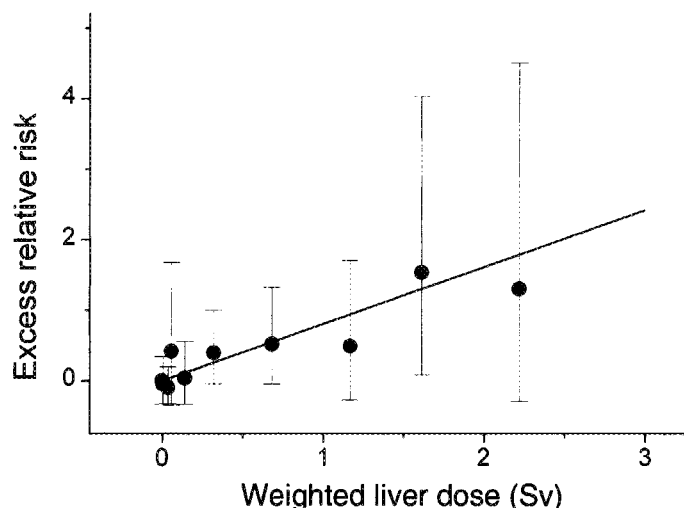
FIG. 1. Excess relative risk for primary liver cancer from atomic bomb radiation. Points are based on fewer, wider dose strata than those used in the analysis to reduce clutter. The fitted lines are from the linear fitted excess relative risk function described in the text and presented in Appendix II.
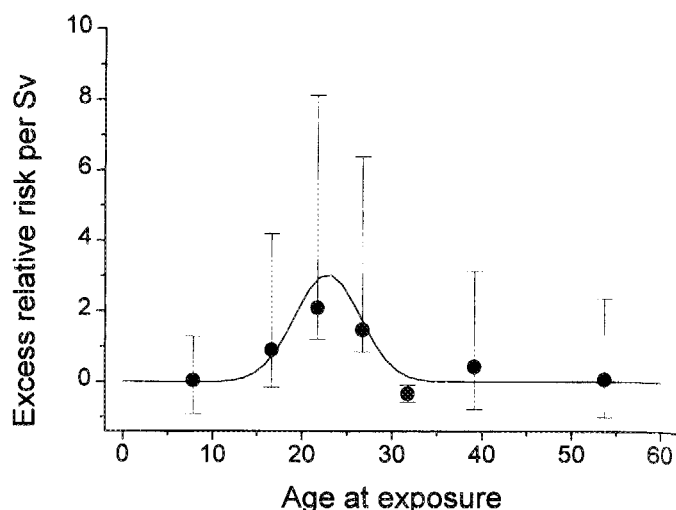

FIG. 2. Dependence on age at exposure of the radiation-related excess relative risk of primary liver cancer at 1 Sv weighted liver dose (RBE = 10). Points are based on fewer, wider age-at-exposure strata than those used in the analysis to reduce clutter. The fitted line is based on an exponentiated linear-quadratic function multiplying the linear excess relative risk function (Appendix II).

Subtypes. The overall rate of hepatocellular carcinoma was 6.44 [4.51, 9.51] times higher than that of cholangiocarcinoma ($P < 0.001$), but cholangiocarcinoma comprised a greater proportion of cases among females than among males. The ratio of the rate for females to that for males, though substantially less than 1.0 for both subtypes, was 3.36 [1.57, 7.31] times higher with cholangiocarcinoma than with hepatocellular carcinoma ($P = 0.0018$).

Rates of both subtypes displayed similar trends with age, but hepatocellular carcinoma appeared at younger ages, perhaps due to its overall greater occurrence. Trends over time, however, were quite different with the two subtypes. Hepatocellular carcinoma, being the predominant subtype, displayed a time trend similar to that of overall liver cancer incidence, but the rate of cholangiocarcinoma declined gradually over the study period. Thus the increase in overall incidence of liver cancer during the study period may be attributed entirely to hepatocellular carcinoma.

Radiation Effects

Crude (unadjusted for city, gender, age or time) excess liver cancer incidence at 1 Sv weighted liver dose in this cohort was 17.4 [6.7, 30.0] ($P < 0.001$) per 100,000 PY; compared to the background incidence of 24.9, the attributable risk at 1 Sv was 41%. Attributable risk was 10% among survivors with non-zero doses. Among all survivors with greater than 1 Gy whole-body doses, attributable risk was 47%.

After allowing for radiation exposure, statistical checks of the adequacy of the model revealed a lack of fit to background incidence for females. This may reflect differences in the two sources of information that contribute to estimation of background incidence: the intercept of the dose re-

sponse reflecting the persons with nonzero dose (all of whom were within 3 km of the hypocenter of the bomb) and the large number of persons with zero dose who were beyond 3 km (out to a distance of 10 km). There is some evidence that background disease and death rates differed between these two subcohorts due to differences in geographical location and potential disease risk factors.[5] The estimate of background incidence among females beyond 3 km was 1.6 [1.1, 2.2] times higher than among females within 3 km ($P = 0.0047$). Because most of the persons within 3 km probably received some radiation exposure (recall that zero dose was assigned to all persons with less than 0.005 Gy), it is not possible to distinguish this geographic difference in background incidence from a protective effect of radiation with relative risk $1.6^{-1} = 0.6$ among females with extremely low doses, but this seems unlikely given its magnitude and the lack of a similar observation in males. All analyses of radiation effects are therefore based on this adjustment to background incidence in females.

Risk of liver cancer increased with radiation dose (Fig. 1). Excess relative risk per sievert based on a linear dose response was 0.81 [0.32, 1.43] ($P < 0.001$). There was no evidence of nonlinearity in the ERR as assessed by the addition of higher-order polynomial terms (for a quadratic term, $P = 0.68$). The ERR was similar ($P = 0.97$ for difference) in males (0.81 [0.28, 1.52]; $P < 0.001$) and females (0.78 [−0.11, 2.51]; $P = 0.10$), although the ERR estimated for females was less precise due to fewer cases. There was a peak in ERR among those exposed around the age of 22–23 (Fig. 2) as seen in the highly significant qua-

dratic component to the age-at-exposure effect modifier ($P = 0.0051$). Most of the excess risk of radiation exposure was evident in those who were exposed between the ages of 10 and 30. There was little excess risk among those exposed over the age of 30 and essentially no excess risk among those exposed over the age of 45 or under the age of 10. We found no evidence of a change in ERR with time since exposure, either with ($P = 0.80$) or without ($P = 0.58$) concurrent adjustment for age at exposure. Furthermore, we found no evidence of interaction between age at exposure and time since exposure ($P = 0.51$).

Because analyses of cancer mortality in the LSS have suggested that gender and age-at-exposure differences in relative risk are not apparent in excess absolute risk due to differences in male–female background rates of most solid cancers, we also fitted excess absolute risk (EAR) models as described elsewhere (15). The EAR depended significantly on gender, age at exposure, and time since exposure. Removal of any of these factors from the term modifying the EAR resulted in a significant lack of fit ($P < 0.001$ for gender and age at exposure; $P = 0.0017$ for time since exposure). The effect of age at exposure on EAR was quadratic as it was with ERR. Despite the greater EAR for people exposed in their late teens and early 20s, there was no evidence that the dependence of excess incidence on time since exposure was a function of age at exposure ($P = 0.49$), nor did the age–time configuration of EAR differ by gender ($P = 0.43$). Furthermore, the joint effect of age at exposure and time since exposure could not be satisfactorily replaced by a function of age alone, as was the case with all solid cancers (15).

Subtype. We attempted to test for a difference in dose response between the two predominant liver cancer subtypes in this cohort—hepatocellular carcinoma and cholangiocarcinoma. However, because of the small background number of cholangiocarcinoma cases, only a few radiation-related excess cholangiocarcinoma cases would be expected if there were no difference in radiation effect by subtype; in fact, no excess cholangiocarcinoma case was observed (not a statistically significant result). There was therefore no statistical power to test for a difference between hepatocellular carcinoma and cholangiocarcinoma dose response. Given that most histologically confirmed cases were hepatocellular carcinoma, the radiation effects reported here would be essentially those for hepatocellular carcinoma alone. However, because of a paucity of confirmed cases of non-hepatocellular carcinoma, the strict interpretation of the present radiation results should be in terms of liver cancer in general rather than hepatocellular carcinoma alone.

DISCUSSION

With the recent increase in liver cancer incidence in Japan (2) and given intrinsic scientific interest in the sensitivity of the liver to the carcinogenic effect of low-LET radiation, it is important to ascertain how radiation affects the risk of

liver cancer for purposes of radiation protection and possibly for risk reduction in the atomic bomb survivor cohort. A radiation effect on liver cancer incidence was reported previously in the Life Span Study cohort of atomic bomb survivors (1). The present analysis provides stronger evidence of that effect through diagnostic review, adjustment for the estimated proportion of incorrect death certificate diagnoses of primary liver cancer, and more thorough analysis of background and radiation-associated incidence. It reveals that the excess risk from radiation exposure—in terms of absolute incidence—was particularly high among males and among those exposed to radiation during their teens and 20s. It remains to ascertain the cause of this apparent age-at-exposure effect, whether it be biological or due to other liver cancer risk factors related to birth cohort—to which males in particular were exposed—which confound or interact with the radiation effect. The analyses could not discriminate possibly differential radiation effects by subtype because of a small number of cases of non-hepatocellular carcinoma, but it is noteworthy that there was a paucity of cholangiocarcinoma and hemangiosarcoma, cancers commonly observed in Thorotrast patients. Whether this is due to a different exposure configuration (Thorotrast deposits in the connective tissue surrounding the intrahepatic bile ducts) or a different mechanism is not clear.

The risk of liver cancer was significantly associated with radiation dose, with a linear excess relative risk of 0.81 per sievert weighted liver dose. To put this into perspective, a weighted liver dose of 1 Sv (relative risk 1.81 for liver cancer) corresponds roughly to a whole-body kerma of 1.2 Gy. The whole-body dose resulting in death to 95% of those exposed within 60 days ($LD_{95/60}$) in this population is of the order of 5.4 Gy, based on a subgroup thought to have well characterized doses (22). An acute whole-body dose of 1 Gy produces probable acute radiation syndrome and borders on possible death due to hematopoietic syndrome (Table 6-1 in ref. 23). Very few persons experienced this level of liver cancer risk; only about 3% of the exposed cohort have estimated whole-body doses at or above 1.2 Gy, due to a high probability of death from radiation and nonradiation causes among persons who were close enough to the bombs to have received large doses. The attributable risk was 10% among all persons with nonzero dose estimates—i.e., 1 out of 10 cases of primary liver cancer diagnosed among LSS cohort members with dose estimates greater than 0.005 Gy may be related to atomic bomb radiation. The LSS cohort was selected to contain a larger proportion of high-dose survivors, so the attributable risk for liver cancer among all directly exposed atomic bomb survivors would be less than 10%.

Patterns of excess risk of liver cancer with radiation exposure were different from those for incidence of all solid cancer in the LSS cohort (1). Relative risk did not depend on gender, but both excess relative risk and excess absolute risk depended on age at exposure. Although the excess relative risk did not depend on gender, the excess absolute risk was higher in males. The shape of the age-at-exposure mod-

ifier of radiation risk suggested that adolescents and young adults were more susceptible to radiation-related liver cancer than children or older adults. No age-at-injection effect was found in the German Thorotrast study (7), but exposure from Thorotrast differs in that it is continuous over many years rather than instantaneous at the age of initial exposure. The age-at-exposure findings are also contrary to those for incidence of all solid cancers combined in the LSS, where excess relative risk is highest in early childhood, decreases with age at exposure, and is higher in females (1). These differences further suggest the presence of underlying factors related to gender and/or birth cohort that might confound or modify the radiation effect on liver cancer.

Use of tobacco or alcohol cannot explain the excess incidence with radiation exposure, because radiation dose is not correlated with amount of use of either of these substances (24). Hepatitis virus infection might confound, or interact with, the radiation effect on liver cancer; a dose-related increase has been reported in prevalence of hepatitis B surface antigen in the sera of atomic bomb survivors (25). If the prevalence of viral hepatitis differs with birth cohort, then this could confound the age-at-exposure interaction with the radiation dose response for liver cancer. The small number of excess cases in females in the present study made it difficult to assess differences in risk modification with gender, so it remains unclear whether the age-at-exposure effect is common to both genders. If modification of the age-at-exposure effect is male-specific, then one might speculate that testosterone—which is related to hepatocellular carcinoma risk in humans (26) and has been shown to modify the carcinogenic effects of aflatoxin in the liver of rats (27)—might be interacting with radiation in liver carcinogenesis during male adolescence. A similar (though unrelated) age-at-injection effect has been reported in dogs (28); young adult beagles were more likely to develop bone cancer from internal irradiation from plutonium-239 and radium-226 than either juveniles or mature adults. On the other hand, whole-body γ irradiation of beagles produced an increase in hemangiosarcomas after exposure during gestation, but not in juvenile or young adult dogs (29).

Rates of hepatitis infection vary dramatically around the world. If the radiation risk and/or age-at-exposure effect in the present analyses were the result partly of confounding by radiation- and birth cohort-related hepatitis infection, or if the joint effect of radiation and hepatitis virus on liver cancer were synergistic, radiation risk estimates derived from the atomic bomb survivor cohort might overstate the risk of liver cancer from radiation in populations residing in regions with low rates of viral hepatitis infection. To help clarify this problem, analyses of possible confounding or interaction between radiation and hepatitis B and C viruses on liver cancer from a nested case–control study conducted in the LSS cohort will be forthcoming.

APPENDIX I

Numbers of Cases and Person-Years Used in the Analysis of Primary Liver Cancer Incidence

	0–39 years attained age				40–49 years attained age				50–59 years attained age			
	0 Sv	<1 Sv	1+ Sv	Total	0 Sv	<1 Sv	1+ Sv	Total	0 Sv	<1 Sv	1+ Sv	Total
Males												
1958–1969	2	1	0	3	1	3	2	6	8	8	2	18
	62,573	91,317	4,267.4	158,157	12,604	16,706	1,224.5	30,534	18,153	24,084	1,390.5	43,627
1970–1979	1	1	0	2	3	14	2	19	6	6	0	12
	25,370	39,144	1,405.8	65,920	20,820	28,732	1,699	51,250	9,134.5	12,306	899.66	22,340
1980–1987	2	0	0	2	5	7	1	13	22	40	4	66
	3,711.6	6,273.6	231.31	10,217	17,394	26,101	914.13	44,409	14,912	20,692	1,300	36,904
Total (year)	5	2	0	7	9	24	5	38	36	54	6	96
	91,654	136,735	5,904.6	234,294	50,817	71,539	3,837.7	126,193	42,199	57,082	3,590.1	102,871
Females												
1958–1969	0	0	0	0	1	1	0	2	3	6	0	9
	77,472	114,812	5,409.1	197,693	33,555	52,020	2,341.9	87,916	32,555	52,853	2,157.6	87,566
1970–1979	0	0	0	0	0	0	0	0	2	2	0	4
	26,437	41,678	1,472.3	69,588	29,781	41,761	2,324.9	73,867	26,747	40,882	1,797.6	69,427
1980–1987	0	0	0	0	2	1	0	3	7	9	0	16
	4,137	6,841.1	197.88	11,176	17,787	27,514	992.33	46,294	23,823	33,044	1,757.5	58,624
Total (year)	0	0	0	0	3	2	0	5	12	17	0	29
	108,046	163,332	7,079.2	278,457	81,123	121,295	5,659.1	208,077	83,126	126,779	5,712.8	215,617
Total (gender)												
1958–1969	2	1	0	3	2	4	2	8	11	14	2	27
	140,045	206,130	9,676.5	355,851	46,158	68,726	3,566.4	118,450	50,708	76,937	3,548.1	131,193
1970–1979	1	1	0	2	3	14	2	19	8	8	0	16
	51,807	80,822	2,878.2	135,508	50,600	70,493	4,023.9	125,117	35,882	53,188	2,697.3	91,767
1980–1987	2	0	0	2	7	8	1	16	29	49	4	82
	7,848.7	13,115	429.19	21,393	35,181	53,615	1,906.5	90,702	38,735	53,735	3,057.5	95,528
Total (year)	5	2	0	7	12	26	5	43	48	71	6	125
	199,700	300,066	12,984	512,751	131,939	192,833	9,496.8	334,270	125,325	183,861	9,302.9	318,489

APPENDIX II

Statistical Models for Background Incidence and Radiation Risk

In this appendix, we present the complete form of models and parameter estimates fitted to the observed liver cancer case and person-year data, describing background incidence as a function of age, gender and calendar time. Excess risk associated with atomic bomb radiation exposure was allowed to be modified by gender, age at exposure, and time since exposure. Grouped points in the figures were obtained by substituting categorical values of appropriate variables; those models are not presented here because making inference about risk in a particular dose or age-at-exposure category is not appropriate given the continuous nature of these variables and the loss of statistical power that results from restricting consideration to one stratum alone.

Background incidence and radiation excess relative risk models were fitted using centered values of age, time, city and gender. For age, time, age at exposure, and time since exposure, we centered the values at the integer nearest to the person-year weighted average for the cohort:

Age:	50 years
Calendar year:	1971
Age at exposure:	24 years
Time since exposure:	26 years

Because all persons were exposed in 1945, average age 50 in 1971 is exactly equal to average age at exposure (24.0) plus average years since exposure (26.0). Age at exposure is perfectly correlated with birth cohort in this population.

Rather than use indicators for one of the two city or gender categories, we used covariates reflecting the proportion in each city or gender category so that estimates would be averaged over city and gender. For city, the proportions and resulting covariates were:

City	Proportion	Covariate (c)
Hiroshima	67.6%	−0.324
Nagasaki	32.4%	+0.676

and for gender:

Gender	Proportion	Covariate (s)
Male	40.4%	−0.596
Female	59.6%	+0.404

The effects of city or gender estimated using these centered covariates have the same interpretation as those estimated using indicator variables (the difference between the two groups) but the interpretation of the other parameters in the model is different because the value "0" for these covariates—and hence the interpretation of parameters for the effects of other factors—reflects the population average rather than a specific group.

The fitted models after adjustment of female, zero-dose background, were as follows (95% likelihood confidence bounds in brackets):

$$\lambda^0_{c,s}(a, y) = \exp \begin{pmatrix} -9.57 & [-9.87, -9.29] & \\ -2.71 & [-3.20, -2.25] & s \\ +0.453 & [0.187, 0.714] & c \\ +7.00 & [5.81, 8.32] & \ln(a) \\ +3.89 & [2.58, 5.27] & s\ln(a) \\ -7.63 & [-9.96, -5.47] & \ln(a)^2 \\ +0.0787 & [0.0662, 0.0916] & y \\ -0.0609 & [-0.0870, -0.0347] & cy \\ +0.485 & [0.150, 0.818] & I_{UF} \end{pmatrix}$$

$$\text{ERR}(d) = 0.806 \quad [0.324, 1.43] \quad d$$

APPENDIX 1
Extended

	60–69 years attained age				70–79 years attained age				80+ years attained age				Total years attained age			
0 Sv	<1 Sv	1+ Sv	Total	0 Sv	<1 Sv	1+ Sv	Total	0 Sv	<1 Sv	1+ Sv	Total	0 Sv	<1 Sv	1+ Sv	Total
8	14	0	22	5	12	0	17	2	2	1	5	26	40	5	71
19,490	26,774	1,408.8	47,672	88,844	13,022	625.31	22,531	1,689.9	2,623	85.977	4,398.9	123,392	174,526	9,002.6	306,921
8	20	1	29	10	15	0	25	6	3	0	9	34	59	3	96
11,699	15,437	894.69	28,031	9,958.7	14,073	628.97	24,661	2,815.4	4,068.8	166.34	7,050.5	79,797	113,761	5,694.5	199,253
15	16	4	35	17	18	1	36	6	5	0	11	67	86	10	163
6,032.5	7,985.9	517.93	14,536	6,352.5	8,263.8	482.04	15,098	3,371.1	4,839.2	167.09	8,377.4	51,773	74,155	3,612.5	129,541
31	50	5	86	32	45	1	78	14	10	1	25	127	185	18	330
37,222	50,196	2,821.4	90,239	25,195	35,359	1,736.3	62,290	7,876.4	11,531	419.41	19,827	254,963	362,442	18,310	635,714
9	7	0	16	6	3	0	9	0	3	0	3	19	20	0	39
26,550	41,705	1,480.7	69,736	12,904	19,845	467.33	33,216	3,388.8	5,120.9	89.091	8,598.8	186,425	286,356	11,946	484,727
5	5	1	11	7	16	1	24	5	3	0	8	19	26	2	47
24,327	39,424	1,570.2	65,320	17,312	27,089	875.97	45,277	5,470.5	8,587.9	160.46	14,219	130,074	199,422	8,201.4	337,697
9	15	2	26	19	17	0	36	11	10	0	21	48	52	2	102
19,050	29,591	1,197.3	49,839	15,795	25,276	890.11	41,962	7,752.7	12,144	338.76	20,235	88,346	134,410	5,373.9	228,130
23	27	3	53	32	36	1	69	16	16	0	32	86	98	4	188
69,927	110,720	4,248.2	184,895	46,011	72,210	2,233.4	120,454	16,612	25,853	588.31	43,053	404,845	620,188	25,521	1,050,553
17	21	0	38	11	15	0	26	2	5	1	8	45	60	5	110
46,040	68,479	2,889.5	117,408	21,788	32,867	1,092.6	55,747	5,078.7	7,743.9	175.07	12,998	309,817	460,882	20,948	791,648
13	25	2	40	17	31	1	49	11	6	0	17	53	85	5	143
36,026	54,861	2,464.8	93,351	27,270	41,162	1,504.9	69,937	8,285.8	12,657	326.81	21,269	209,871	313,182	13,896	536,950
24	31	6	61	36	35	1	72	17	15	0	32	115	138	12	265
25,083	37,577	1,715.2	64,375	22,148	33,540	1,372.1	57,060	11,124	16,983	505.85	28,613	140,119	208,565	8,986.4	357,671
54	77	8	139	64	81	2	147	30	26	1	57	213	283	22	518
107,149	160,916	7,069.6	275,134	71,206	107,569	3,969.7	182,745	24,488	37,384	1,007.7	62,880	659,808	982,629	43,831	1,686,269

without effect modification and

$$\lambda_{c,s}^{0}(a, y) = \exp\begin{pmatrix} -9.57 & [-9.86, -9.29] & \\ -2.74 & [-3.23, -2.28] & s \\ +0.432 & [0.167, 0.693] & c \\ +6.96 & [5.77, 8.26] & \ln(a) \\ +3.95 & [2.64, 5.33] & s\ln(a) \\ -7.07 & [-9.40, -4.91] & \ln(a)^2 \\ +0.0756 & [0.0629, 0.0887] & y \\ -0.0598 & [-0.0859, -0.0336] & cy \\ +0.449 & [0.119, 0.776] & I_{UF} \end{pmatrix}$$

$$\text{ERR}(d) = 3.33 \quad [1.22, 6.73] \quad d$$

$$\phi(e) = \exp\begin{pmatrix} -0.0836 & [-0.316, 0.086] & e \\ -0.0385 & [-0.0858, -0.0073] & e^2 \end{pmatrix}$$

with modification of radiation risk by age at exposure. The notation I_{UF} represents the indicator of zero-dose females (see text). The ERR in the above formula is large because age at exposure is centered at age 24, near the peak sensitivity (Fig. 2).

Because it was not possible to discriminate radiation effects by subtype, the models fitted to subtype included only a simple dose–response adjustment which should not be directly interpreted or compared to that estimated for all liver cancer combined. The fitted subtype model was:

$$\lambda_{c,s}^{0}(a, y, \text{subtype})$$

$$= \begin{pmatrix} 12.9 \times 10^{-5} & \text{(hepatocellular carcinoma)} \\ [10.4, 15.8] & \\ & \text{or} \\ 1.81 \times 10^{-5} & \text{(cholangiocarcinoma)} \\ [0.98, 2.98] & \\ & \text{or} \\ 4.86 \times 10^{-5} & \text{(other/unknown)} \\ [3.42, 6.69] & \\ & \text{or} \\ 2.74 \times 10^{-5} & \text{(DCO)} \\ [1.86, 3.93] & \end{pmatrix}$$

$$\times \exp\begin{pmatrix} +0.401 & [0.155, 0.643] & c \\ -1.84 & [-2.11, -1.59] & s \\ +0.882 & [0.126, 1.65] & sI_{\text{cholang}} \\ +3.54 & [2.78, 4.34] & \ln(a) \\ +3.64 & [2.34, 5.01] & s\ln(a) \\ +4.34 & [1.73, 7.19] & I_{\text{cholang}}\ln(a) \\ +2.28 & [0.954, 3.80] & I_{DCO}\ln(a) \\ -9.06 & [-11.7, -6.63] & \ln(a)^2 \\ +6.06 & [0.309, 10.9] & I_{DCO}\ln(a)^2 \\ +0.0639 & [0.0487, 0.0795] & y \\ -0.0580 & [-0.0832, -0.0327] & cy \\ -0.0918 & [-0.137, -0.0477] & I_{\text{cholang}}y \\ +0.0832 & [0.0521, 0.116] & I_{\text{oth/unk}}y \end{pmatrix}$$

$$\text{ERR}(d) = 0.658 \quad [0.230, 1.21] \quad d$$

where "other/unknown" includes all cases with histological or clinical diagnosis that were not hepatocellular carcinoma or cholangiocarcinoma,

or where the review panel could not determine subtype (it is likely that most of the cases of unknown subtype were hepatocellular carcinoma given its preponderance among cases with known subtype). The indicator I_{cholang} represents cholangiocarcinoma subtype, $I_{\text{oth/unk}}$ is the indicator of the other/unknown subtype, and I_{DCO} is the indicator of cases identified through death certificate only.

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